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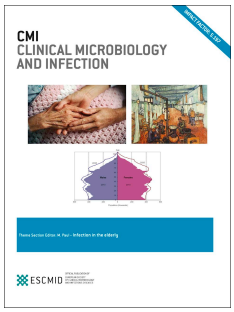

Efficacy of favipiravir in adults with mild COVID-19: a randomized, double-blind, multicenter, placebo-controlled trial clinical trial

Mohammad Bosaeed, Ahmad Alharbi, Ebrahim Mahmoud, Sanaa Alrehily, Mohannad Bahlaq, Zied Gaifer, Hanan Alturkistani, Khaled Alhagan, Saad Alshahrani, Ali Tolbah, Abrar Musattat, Maha Alanazi, Raniah Jaha, Khizra Sultana, Hajar Alqahtani, Kholoud Al Aamer, Saud Jaser, Abdulrahman Alsaedy, Ayoub Ahmad, Mohammed Abalkhail, Sameera AlJohani, Majed Al Jeraisy, Sultan Almaziad, Nahlah Albaalharith, Khaled Alabdulkareem, Abdulmajeed Alshowair, Naif Khalaf Alharbi, Fahad Alrabiah, Majid Alshamrani, Omar Aldibasi, Ahmed Alaskar

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Efficacy of Favipiravir in Adults with Mild COVID-19: a randomized, double-blind, multicenter, placebo-controlled trial Clinical Trial

Mohammad Bosaeed[1,2,3]; Ahmad Alharbi[1,2,3] ; Ebrahim Mahmoud[1,2,3]; Sanaa Alrehily[4]; Mohannad Bahlaq[5]; Zied Gaifer[6]; Hanan Alturkistani[7]; Khaled Alhagan[3]; Saad Alshahrani[5]; Ali Tolbah[5]; Abrar Musattat[3]; Maha Alanazi[3]; Raniah Jaha[3]; Khizra Sultana[3]; Hajar Alqahtani[8]; Kholoud Al Aamer[8]; Saud Jaser[8]; Abdulrahman Alsaedy[1,2,3]; Ayoub Ahmad[1]; Mohammed Abalkhail[9]; Sameera AlJohani[3,10,11]; Majed Al Jeraisy[3,8,12]; Sultan Almaziad[9]; Nahlah Albaalharith[13]; Khaled Alabdulkareem[5]; Abdulmajeed Alshowair[5]; Naif Khalaf Alharbi[2,3]; Fahad Alrabiah[14]; Majid Alshamrani[2,3,9]; Omar Aldibasi[3,15]; Ahmed Alaskar[2,3,16]

Affiliations:

[1]Department of Medicine, King Abdulaziz Medical City - Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia.

[2]College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.

[3]King Abdullah International Medical Research Center, Riyadh, Saudi Arabia.

[4]King Fahad Hospital - Almadinah, Ministry of Health, Saudi Arabia.

[5]Deputyship for Primary Health Care, Ministry of Health, Riyadh, Saudi Arabia.

[6] Department of Medicine, Prince Mohammed Bin Abdul Aziz Hospital - Almadinah, Ministry of National Guard Health Affairs, Saudi Arabia.

[7]King Abdullah Medical City - Makkah, Ministry of Health, Saudi Arabia.

[8]Pharmaceutical Care Department, King Abdulaziz Medical City, Riyadh, Saudi Arabia.

[9]Infection Prevention and Control Program, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia.

[10]Department of Pathology & Laboratory Medicine, King Abdulaziz Medical City, Riyadh, Saudi Arabia.

[11]College of Science and Health Professions, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.

[12]College of Pharmacy, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.

[13] Department of Nursing, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia.

[14]King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

[15]College of Dentistry, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

[16]Department of Oncology, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia.

Correspondence to:

Mohammad Bosaeed.

Infectious Diseases Division, Department of Medicine, King Abdulaziz Medical City, Riyadh 11426, Saudi Arabia. bosaeedmo@ngha.med.sa Tel: 966(11)4294622, Fax: 966(11)4294440

Abstract

Objective: To evaluate whether favipiravir reduces the time to viral clearance as documented by negative SARS-CoV-2 RT-PCR in mild COVID-19 cases compared to placebo.

Methods: In this randomized, double-blinded, multicenter, and placebo-controlled trial, adults with PCR confirmed mild COVID-19 were recruited in an outpatient setting at seven medical facilities across Saudi Arabia. Participants were randomized in a 1:1 ratio to receive either favipiravir 1800 mg by mouth twice daily on day one followed by 800 mg twice daily (n=112) or a matching placebo (n=119), for a total of 5 to 7 days. The primary outcome was the effect of favipiravir on reducing the time to viral clearance (by PCR test) within 15 days of starting the treatment compared to the placebo group. The trial included the following secondary outcomes: symptom resolution, hospitalization, ICU admissions, adverse events, and 28-day mortality.

Results: 231 patients were randomized and began the study (median age, 37 [interquartile range: 32-44] years; 155 [67%] men), and 112 (48.5%) were assigned to the treatment group and 119 (51.5%) into the placebo group. The data and safety monitoring board (DSMB) recommended stopping enrollment because of futility at the interim analysis. The median time to viral clearance was 10 (IQR: 6-12) days in the favipiravir group and 8 (IQR: 6-12) days in the placebo group, with a hazard ratio of 0.87 for the favipiravir group (95% CI 0.571 to 1.326; p-value =0.51). The median time to clinical recovery was 7 days (IQR: 4-11) in the favipiravir group and 7 days (IQR: 5-10) in the placebo group. There was no difference between the two groups on the secondary outcome of hospital admission. There were no drug-related severe adverse events.

Conclusion: In this clinical trial, favipiravir therapy in mild COVID-19 patients did not reduce the time to viral clearance within 15 days of starting the treatment.

Keywords: Favipiravir; Mild COVID-19; Non-Severe SARS-CoV-2; clinical trial

Clinical Trial Registration: ClinicalTrials.gov identifier (**NCT04464408**):

https://clinicaltrials.gov/ct2/show/NCT04464408

Introduction

As of December 20, 2021, COVID-19 has affected more than 275 million people worldwide and caused nearly five million deaths.[1] Since the WHO has declared COVID-19 as pandemic, researchers have studied potential effective therapies.[2,3,4,5,6] Favipiravir is an RNA-dependent RNA polymerase (RdRp) inhibitor with activity against influenza virus. It has also shown activity to block the replication of other RNA viruses.[7,8] SARS-CoV-2 is a positive-sense single-strand RNA virus, making its RdRp a potential target that favipiravir can block.[9] Favipiravir showed promising results in mild to moderate COVID-19 patients in earlier studies[10-12] and has been listed as a possible treatment in different regimen protocols for mild to moderate COVID-19 cases by various health regulators and agencies.[13,14] Starting mild COVID-19 treatment early may prevent progression into a more severe form of the disease.[15,16]

To evaluate the safety and efficacy of favipiravir monotherapy in treating mild COVID-19, we conducted a multicenter placebo-controlled randomized trial in Saudi Arabia (Avi-Mild-19).

Methods

Study design

The trial enrolled patients from seven community medical centers and ambulatory care centers in Saudi Arabia. The trial was sponsored by King Abdullah International Medical Research Center (KAIMRC). Ethical approval was obtained from the Institutional Review Board (IRB) at the Ministry of National Guard-Health Affairs (MNGHA) and the Ministry of Health (MOH). The trial was overseen by an independent data and safety monitoring board (DSMB). The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice.

Randomization and blinding

Patients were randomized in a 1:1 ratio to oral favipiravir or placebo. The randomization schedule was generated using the *PLAN Procedure (SAS)* with a block size of four, stratified by study site. The generated list was embedded in the Research Electronic Data Capture (REDCap) system to ensure allocation concealment. Participants, investigators, and study staff remained unaware of the treatment assignment. The Sponsor's investigational drug unit, which is not part of the study team, held the information for treatment allocation.

Patients

The study population was patients, aged 18 years and above, from community settings diagnosed with mild COVID-19 (confirmed by positive PCR test for SARS2-CoV), and were enrolled within 5 days of disease onset. Mild COVID-19 case defined as a patient with mild illness (with or without respiratory symptoms), oxygen saturation >94% at room air, and can be managed at home with appropriate therapy. Mild illness can include symptoms of uncomplicated upper respiratory tract viral infection such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache. Rarely, patients may also present with diarrhea, nausea, and vomiting.

Key exclusion criteria included hospitalized moderate or severe COVID-19 cases, pregnant or breastfeeding females, those who used favipiravir or participated in other interventional drugs clinical study within 30 days prior to the first dose of the study treatment. The exclusion criteria also included major comorbidities such as hematologic malignancy, advanced (stage 4-5) chronic kidney disease (including dialysis therapy), severe liver damage (Child-Pugh score C or AST> 5 times the upper limit), HIV. Patients with history of gout or hyperuricemia (two times above the upper limit of normal), patients with sensitivity/allergy to favipiravir, and cases with clinical prognostic non-survival, palliative care, or in a deep coma were also excluded.

Procedure

Study subjects were randomized to either receive favipiravir 1800 mg (9 tablets) twice daily as a loading dose on day one followed by 800 mg (4 tablets) twice daily as a maintenance dose for a total duration of 5 to 7 days of therapy or matching placebo. Follow-up was started on the second day of enrollment by a research coordinator or a study physician through daily phone calls for 14 days or until reaching secondary endpoints. The follow-up also assessed subjects' compliance, health status, and clinical symptoms. A final follow-up phone call was subsequently conducted on day 28 for all patients. Patients were required to visit study sites on days 5±1 day, 10±1 day, 15±2 days for nasopharyngeal/ oropharyngeal swabs and blood tests. The swabs were used for detecting SARS-CoV-2 by the Reverse Transcriptase polymerase chain reaction (RT-PCR) to document the time of viral clearance (negative PCR) or viral infection persistence (positive PCR).

Efficacy and Safety assessment

The primary endpoint of this study was time from start of treatment to viral clearance defined as the conversion of SARS-CoV-2 RT-PCR from positive to negative within 15 days as described in procedures.

Prespecified secondary endpoints included time from the start of treatment (favipiravir or placebo) to clinical recovery with normalization of fever, respiratory symptoms, and relief of cough (or other relevant symptoms at enrollment) that is maintained for at least 72 hours, need to use antibiotics within 15 days after starting the medicine, progression of disease in a 28-day period including hospitalization, ICU admissions with or without ventilation requirements, and 28-day mortality. Additional secondary safety endpoints included the occurrence of allergic reactions, medication intolerance, and liver toxicity in subjects within 15 days of taking the study drug.

Statistical analysis

A one-sided test of whether the hazard ratio HR is 1 with an overall sample size of 576 subjects (288 are in the control group and 288 in the treatment group) achieve 90% power at a 0.025 significance level

when the HR is 1.330. An interim analysis was planned once after the recruitment and follow-up of 40% of the total number of subjects (i.e. 230 subjects). The interim analysis was designed to test for early stopping for futility or efficacy and sample size re-estimation. The decision rule based on the study protocol were (1) stop the trial for early efficacy if the interim analysis p-value < 0.01, (2) stop the trial for futility if the interim analysis p-value ≥ 0.25, or (3) declare the trial significant if the sum of the interim analysis and final stage p-values < 0.1832.[12]

The survival analysis method for interval-censored data was used to analyze the primary endpoints due to the nature of the data collection (i.e., subjects' clearance is observed during specific follow-up time). Results were reported in terms of HR and 95% CI and one-sided p-value based on the Cox proportional hazard model. A similar analysis was conducted for the secondary outcome of the time to symptoms resolved of the two treatment groups at 15 days. Analysis for adverse events (AEs) was primarily descriptive using the proportion of subjects who experienced AEs. More detailed analyses methods are included in the statistical analysis plan (see Supplementary Material).

Stopping the Trial:

Data and Safety Monitoring Board (DSMB) had requested an assessment of conditional power to form a recommendation on continuing the trial upon recruiting and following-up of more than 40% of the estimated study sample size (231 patients). On September 21, 2021, the DSMB reviewed the interim analysis result and recommended stopping the trial due to futility based on the calculated p-value.

Results

Participants

Between July 23, 2020 and August 4, 2021, 245 patients were randomized. Among those, 231 began the study and received the assigned treatment (112 in the favipiravir group and 119 in the placebo group). Of

the 14 patients excluded after randomization, one did not meet eligibility criteria, and 13 withdrew consent; none received the study treatment (Figure 1).

Participants had a median age of 37 (IQR: 32-44) years, and 155 (67%) were men. Overall, one patient had cardiovascular disease, 14 (6%) had hypertension, 25 (10.8%) had diabetes, and 8 (3.4%) had asthma at the baseline. Approximately 39 (16.8%) were obese (body mass index >30). Baseline characteristics were well balanced between groups (Table 1) with a minor insignificant imbalance in BMI, diabetes, and smoking.

In the favipiravir group, 101 (90%) completed treatment duration (minimum five days total). Discontinuing the treatment before five days in 10% of subjects was due to adverse events in two patients, unexplained in three patients, and hospitalization in six patients. Of 119 patients in the placebo group, 113 (94.9%) completed the assigned treatment duration; discontinuing the placebo before five days was due to adverse events in two patients, unexplained in three patients, and hospitalization in one patient. Nonetheless, all patients were evaluated for the outcome on day 28.

Efficacy

The primary outcome was ascertained in all patients in the modified intention-to-treat (mITT) population. Patients who had viral clearance within 15 days were 42 of 112 (37.5%) in the favipiravir group and 49 of 119 (41.1%) in the placebo group. Time to viral clearance was not significantly different between the two groups (Figure 2), with a median of 10 (IQR: 6-12) days in the favipiravir group and 8 (IQR: 6-12) days in the placebo group (HR=0.87; 95% CI 0.571 to 1.326; p-value =0.51).

The number of patients with COVID-19 related hospital admission was six (5.3%) in the favipiravir group and two (1.6%) in the placebo group (p-value =0.16). Furthermore, the median time to clinical recovery was 7 days (IQR: 4-11) in the favipiravir group and 7 days (IQR: 5-10) in the placebo group (95% CI 0.639 to 1.250; p-value =0.51), (see Supplementary Material Figure S1). There was no difference in the resolution of any symptoms or the need to use antibiotics.

Safety

Adverse events were experienced by eight (7.1%) patients in the favipiravir group and seven (5.8%) in the placebo group; however, none were serious according to the protocol definition. Adverse events leading to discontinuation of the study were only recorded in four patients, two in each group. Discontinuations were mainly due to gastrointestinal symptoms, including nausea, vomiting, and abdominal pain. Adverse events were more common in the favipiravir groups than in the placebo group, including skin rash, respiratory symptoms, and vomiting (see Supplementary material Table S2).

Significant elevations in the levels of liver enzymes (AST and ALT) were noted more in the favipiravir group; all returned to the normal range by the day 28 follow-up. Three patients in the favipiravir group and one in the placebo group had worsened kidney functions with a drop in creatinine clearance below 60 mL/min. No patient had creatinine clearance less than 30 mL/min or required hemodialysis in our study.

By day 28 follow-up, emergency department/urgent care visits in the favipiravir group were more than in the placebo group; 11 (9.8%) and 7 (5.8%), respectively ($p = 0.36$). The eight hospitalizations in both groups were all related to disease progression and none were related to treatment adverse events. No other serious adverse events were reported and there were no deaths in either of the study groups.

Subgroup and Exploratory Analyses

The intervention did not impact on the primary outcome when age, sex, obesity, and symptoms duration prior to the enrollment were considered as subgroups. In the subgroup of those who used the favipiravir within 48-hours of the symptoms onset, clinical improvement or the time to viral clearance were not significantly different (Figure 3; Figure S2 in supplementary material).

Discussion

In this double-blinded, placebo-controlled, randomized trial, favipiravir was not associated with a faster viral clearance nor a better clinical outcome when initiated in the first five days of the onset of the COVID-19 symptoms.

Several antiviral agents with the potential ability to treat SARS-CoV-2 infections have been studied including remdesivir, hydroxychloroquine, lopinavir-ritonavir, and interferon in the solidarity trial and other trials and were found ineffective.[5,17,18] Due to the lack of impact on COVID-19 mortality of the studied agents, evaluating other potential antivirals like favipiravir in a prospective setting was needed.[19,20] A randomized study using favipiravir in mild-to-moderate COVID-19 patients failed to show a statistical significance on the primary endpoint of time to RT-PCR negativity. In that trial, a significant improvement in reducing the time to clinical recovery was observed; the difference tends to disappear in mild cases where median time to clinical recovery was 3 versus 4 days in favipiravir and control groups, respectively.[11] Contrary to these findings, a more recent randomized clinical trial noted positive results of favipiravir treatment in moderate COVID-19.[21] The primary endpoint of this single-blinded trial of 156 patients was a composite of clinical, radiological, and microbiological outcomes. We previously reported the efficacy of combined favipiravir and hydroxychloroquine in treating moderate to severe COVID-19 cases in a prospective randomized controlled trial. When compared to the standard of care, the combination was found to be ineffective using a seven-category ordinal scale for clinical improvement.[22] The previous trial focused on a moderate to severe cases and did not evaluate single favipiravir treatment. The discrepancies in results from favipiravir trials can be due to many factors such as study designs, populations, and ethnicity; possibly, the inconsistency in defining COVID-19 severity could have also impacted the variability of reported results.

Two systematic reviews did not reveal any significant difference between favipiravir and comparators on fatality rate and mechanical ventilation requirement,[23,24] but noted that it may promote viral clearance within 7 days and clinical improvement within 14 days of treatment, especially in mild-to-moderate COVID-19 cases.[24] Data on the early initiation of antiviral therapy, which could lead to a rapid and significant improvement of viral infections, supported our current trial.[25,26]

Our data provide consistent findings with previous studies on the absence of favipiravir activity/effect in all examined endpoints (viral clearance, time to clinical improvement, and hospital admission), outweighing the lack of favipiravir effectiveness in this population. Taken together, it could be extrapolated that there is no favipiravir effect on COVID-19 regardless of the disease severity.

In terms of safety, adverse events reported in our trial were similar to previous reports.[27-29] Unlike our study, some trials reported chest pain and increase in triglyceride levels as adverse events following favipiravir treatment.[27, 28, 30] Other trials also reported hyperuricemia as a non-serious adverse drug reaction secondary to favipiravir[29,30] but uric acid was not part of our follow up laboratory testing as we excluded all patients with gout disease based on the study protocol. However, although no serious adverse events were observed in either group, the daily pill burden was a major challenge. The recommended daily doses to achieve acceptable plasma concentrations are 3600 mg (18 tablets) on the first day and 1600 mg (8 tablets) on the following days. Such number of pills with unproven benefits can be undesirable due to the difficulties in administration and possible adverse effects.

The study has also encountered some limitations due to the sample size, noncompliance, missing data, and withdrawal after randomization. Nevertheless, the study showed an almost certain result of non-efficacy of the investigational drug. Viral clearance as a primary endpoint was used commonly in viral clinical trials, including prior influenza clinical trials. Since more than 80% of the COVID-19 disease would not progress to severe illness or require hospitalization, clinical improvement might not reflect the efficacy of the antiviral where symptom resolution occurs without therapy and can be very subjective. The study team favored a more objective outcome of the viral clearance. Furthermore, reducing viral clearance could strongly impact disease transmission, a critical infection control measure. The study is still considered underpowered for the secondary clinical endpoints, but it can help design future clinical trials and generate valuable systematic reviews and meta-analyses. To our knowledge, this is the largest double-blinded, placebo-controlled, randomized trial to evaluate the efficacy of favipiravir monotherapy in treating mild COVID-19 patients. Additionally, our trial adds to the growing body of evidence on the

clinical/microbiological benefits of re-purposing antiviral therapy, particularly favipiravir, for SARS-CoV-2 infections.

In conclusion, this randomized double-blinded placebo-controlled clinical trial found no clinical/virological benefit in treating mild COVID-19 patients with favipiravir. The trial result may influence decisions to remove favipiravir from national protocols for COVID-19 treatment.

Transparency declaration

All authors declare no conflict of interests.

Author Contributions:

Bosaeed M, Alharbi A, Mahmoud E, and Abalkhail M jointly formed the study concept and design,. Alrehily S, Bahlaq M, Gaifer Z, Alturkistani H, Alhagan K, Alshahrani S, Tolba A participated in enrollment and data collection. Alharbi A, Bosaeed M and Aldibasi O participated in the acquisition, analysis, or interpretation of data. Alqahtani H, Almaziad S, Alharbi A, Aldibasi O, Mahmoud E, Alharbi N critically reviewed the manuscript. Aldibasi O performed the statistical analysis. Bosaeed M obtained

the funding. Musattat A, Alanazi M, Jaha R, Sultana K, Albaalharith N, Al Aamer K, Jaser S, Alsaedy A, Alrabiah F, Alshamrani M, Al jeraisy M, and Aljohani S contributed in administrative, technical and material support. Alaskar A, Alabdulakreem K, Alshowair A and Bosaeed M participated in supervision.

All authors critically revised the report and approved the final version to be submitted for publication. The corresponding author confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication

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All the authors have full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data sharing:

The study Statistical Analysis Plan is available with this publication as part of the supplementary material. Individual participant data are available upon request addressed to the corresponding author, and after approval of a proposal, can be shared within a secure online platform. A data-sharing agreement will be needed.

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Table 1. Demographic, Clinical, and Laboratory Baseline Characteristics

	Participants, No. (%)	
Characteristic	**Favipiravir (n=112)**	**Placebo (n=119)**
Sex		
Male	72 (64.2)	83 (69.7)
Female	40 (35.7)	36 (30.2)
Age, Median (IQR), y	37 (31.5-45)	36 (32-44)
BMI, ≥30 kg/m^2	24 (21.4)	15 (12.6)
Comorbidities and Risk Factors		
Hypertension	8 (5)	6 (7)
Cardiovascular disease	0	1 (0.8)
Chronic pulmonary disease	1(0.8)	1(0.8)
Asthma	5 (4.4)	3 (2.5)
Chronic neurological disorder	1 (0.8)	0
Rheumatologic/Auto-immune disorder	0	1 (0.8)
Diabetes with complications	2 (1.7)	1 (0.8)
Diabetes without complications	13 (11.6)	9 (7.5)
Smoking	4 (3.5)	8 (6.7)

Time from symptoms onset to randomization, Median (IQR), d	3 (2- 4)	3 (2- 4)
Laboratory variables		
White blood cell count, median (IQR), $\times 10^9$ /L	5.19 (4.1 - 6.3)	5.14 (4- 6.8)
Lymphocyte count, median (IQR), $\times 10^9$/L	1.9 (1.4 – 2.4)	1.9 (1.5 – 2.4)
Hemoglobin, median (IQR), g/dL	15 (13.6 – 15.7)	15 (14 – 16.2)
Platelets count, median (IQR), $\times 10^9$/L	231 (193 - 277)	244 (211 - 289)
Serum creatinine, μmol/L, median (IQR)	76 (64 – 85)	74 (64 - 84)
Total Bilirubin, μmol/L, median (IQR)	8.2 (5.3 - 11.7)	8.3 (5.7 – 11.7)
Aspartate aminotransferase, median (IQR), U/L	24 (20 - 31)	25 (20 – 32.7)
Alanine aminotransferase, median (IQR), U/L	28 (20 – 40.3)	30.8 (20 - 51)

Table 2. Clinical Outcomes

Outcome	Favipiravir N=112 (%)	Placebo N-119 (%)
Primary Outcome		
Time to viral clearance**,** Median (IQR), d	10 (6-12)	8 (6-12)
Secondary Outcome		
Time to clinical recovery, median (IQR), d	7 (4-11)	7 (5-10)
Need to use antibiotics	8 (7.1)	5 (4.2)
Complications:		
ER visits	11 (9.8)	7 (5.8)
hospitalization	6 (5.3)	2 (1.6)
ICU admission	3 (2.6)	0
Bacterial pneumonia	1 (0.8)	0
28-day mortality	0	0

FIGURE LEGENDS

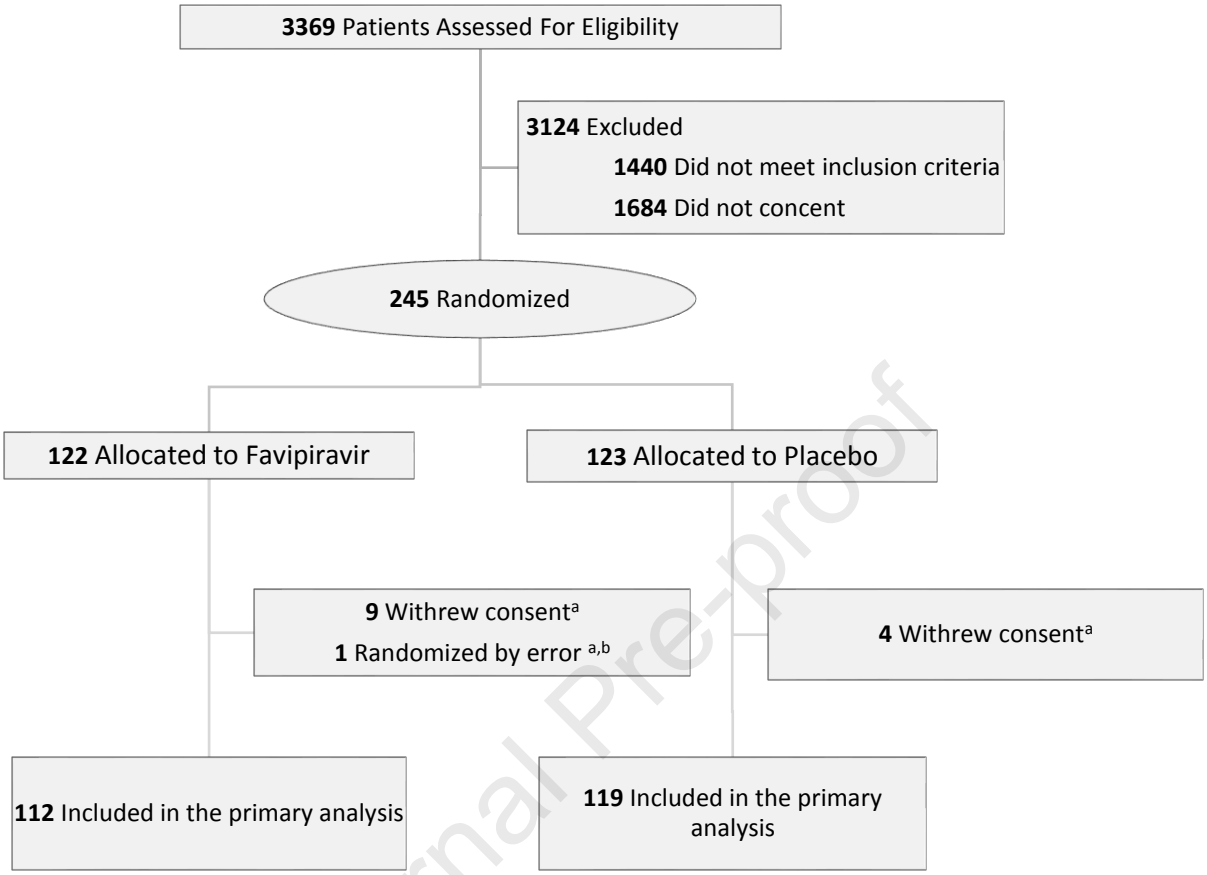
Figure 1. Study Flow Diagram

Figure 2. Time to viral clearance in the mITT analysis.

The survival curves are survival function (Kaplan-Meier) curves with a P-value calculated by the log-rank test is showing Time to viral clearance in the modified Intention to Treat population. There was no difference between the treatment and placebo groups in time of SARS-CoV-2 PCR converging from positive to negative. Patients were followed for 15 days post-randomization.

Figure 3. Time to viral clearance in subgroups.

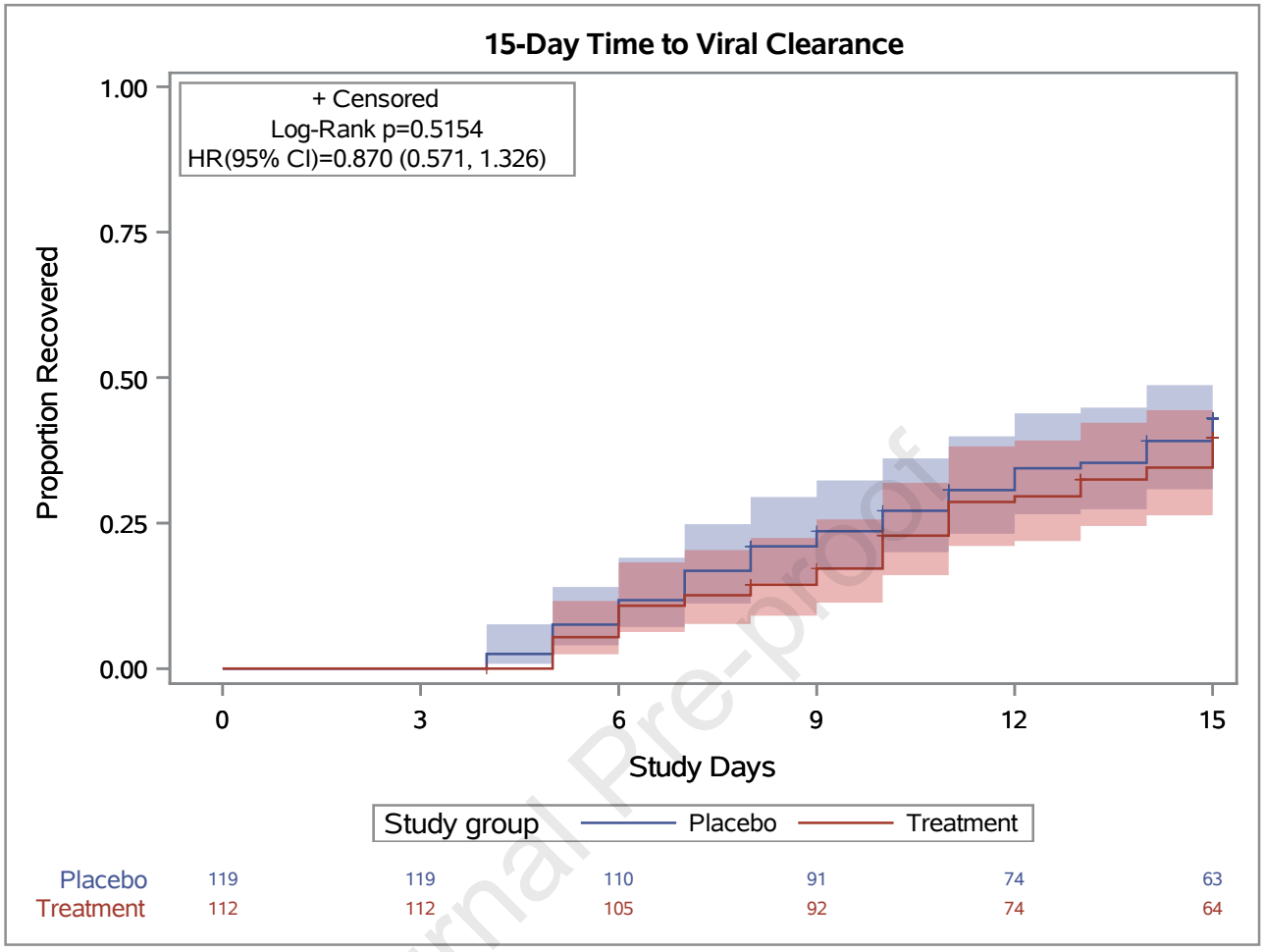
Figure 1. Study Flow Diagram



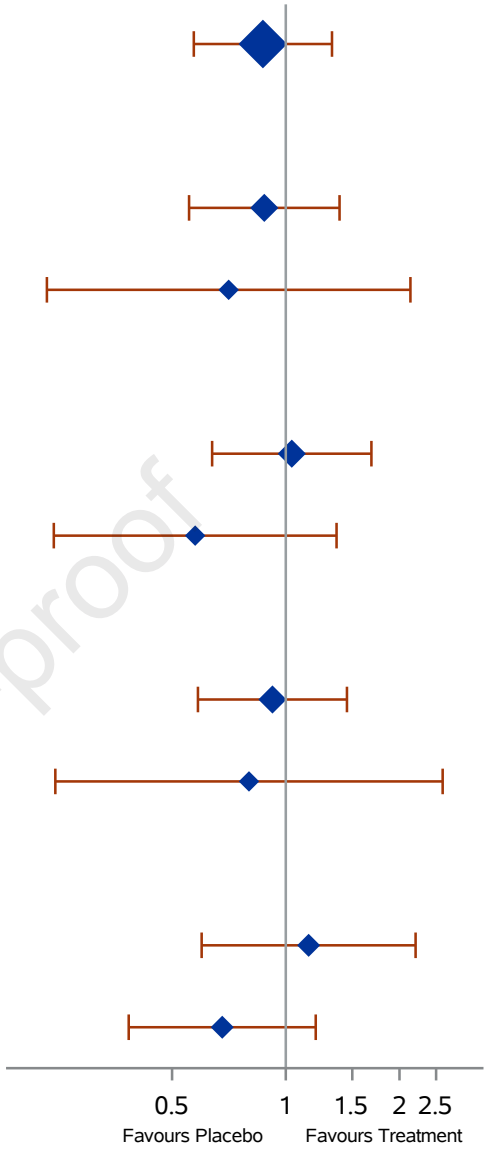
[a] Did not receive the assigned treatment

[b] Did not meet the eligibility criteria on the day of randomization

The LIFETEST Procedure



Subgroups	Placebo Events/N (%)		Treatment Events/N (%)		HR (95% CI)	P-value*
Overall	49/119	(41.2%)	42/112	(37.5%)	0.87(0.57, 1.33)	
Age Group						0.7074
<50 years	43/108	(39.8%)	34/93	(36.6%)	0.88(0.55, 1.39)	
>=50 years	6/11	(54.5%)	8/19	(42.1%)	0.71(0.23, 2.14)	
Sex						0.4494
Male	36/83	(43.4%)	33/72	(45.8%)	1.04(0.64, 1.69)	
Female	13/36	(36.1%)	9/40	(22.5%)	0.58(0.24, 1.36)	
BMI						0.8774
=<30	44/104	(42.3%)	35/88	(39.8%)	0.92(0.59, 1.45)	
>30	5/15	(33.3%)	7/24	(29.2%)	0.80(0.25, 2.60)	
Symptoms onset to enrollment						0.3773
=<48 hr	17/39	(43.6%)	22/45	(48.9%)	1.15(0.60, 2.21)	
>48 hr	32/80	(40.0%)	20/67	(29.9%)	0.68(0.38, 1.20)	



*P-value is the test of interaction between treatment and each subgroup unadjusted for multiplicity.